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EXAMINER

MCGILLEM, LAURA L

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/759,526	Applicant(s) GEORGE ET AL.	
	Examiner Laura McGillem	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 May 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-62 is/are pending in the application.
- 4a) Of the above claim(s) 29-62 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 November 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Priority

This application receives priority to Provisional Application No. 60/509,061, filed 01/22/2003. It is noted that Provisional Application No. 60/509,061 was originally filed as Application No. 10/350,313, which was converted to a provisional application by petition.

Election/Restrictions

Applicant's election of Group I (claims 1-28) in the reply filed on 5/15/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election of the species "Fibroblast" in the reply filed on 5/15/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 29-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/15/2006. Claims 1-28 are under examination.

Claim Objections

Claim 8 is objected to because of the following informalities: it recites the phrase "the group consisting of a comprises a" which is grammatically incorrect; it recites the phrase "selected form the group" and the word "form" appears to be a typographical error; and the word "epithelial" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 recites the limitation "the Angiotensin Receptor" and is dependent on claim 1. There is insufficient antecedent basis for this limitation in the claim. Claim 1 does not recite an Angiotensin receptor.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of acceleration of the cell cycle in fibroblasts using radio frequency radiation, *in vitro* method of activation of a cell cycle regulator, a signal transduction protein, a transcription factor, a DNA synthesis protein and a receptor in fibroblasts keratinocytes using radio frequency radiation, does not reasonably provide enablement for an *in vivo* method for accelerating the cell cycle,

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comprising delivering to a cell an effective amount of any type of electromagnetic energy, or enablement for an *in vivo* method for activating a cell cycle regulator, signal transduction protein, transcription factor, DNA synthesis protein or a receptor *in vivo*, or enablement for an *in vivo* method for inhibiting an angiotensin receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

1) Scope of the claims. The claims are drawn to methods for accelerating the cell cycle comprising delivering an effective amount of electromagnetic energy to accelerate the cell cycle both *in vitro* and *in vivo*. Electromagnetic energy encompasses energy with wavelengths in the region of the spectrum selected from the group consisting of X-ray radiation, ultraviolet radiation, visible radiation, infrared radiation, microwave radiation and radiofrequency radiation, which is a very large genus of types of electromagnetic energy. The claims are drawn to methods comprising activation of a cell cycle regulator, a signal transduction protein, a transcription factor, a DNA synthesis

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protein and a receptor, which each encompass extremely large groups of proteins.

Since the scope of electromagnetic energy to be administered is very broad and the scope of the proteins to be activated in order to activate a complex process such as the cell cycle, the scope of the claimed methods is extremely broad.

2) State of the Art. The skilled artisan would recognize that the cell cycle is an extremely complex process that requires multiple signaling and effector molecules. Otter et al (Clin. Orthop. Relat. Res. 1998, Vol. 355 Suppl, pages 90-104) teach the beneficial effects of electromagnetic fields in bone repair and teach that pulsed electromagnetic fields have become the industry standard for electromagnetic bone healing devices (see page S93, right column, 1st paragraph). Otter et al teach that numerous gene transcription effects have been reported for various electromagnetic fields with any biologic systems and that the state of the biologic system to which the electromagnetic energy will be delivered must be taken into account in order to understand the mechanisms of the complex signals involve in bone healing (see page S94, right column, 2nd paragraph). Otter et al disclose difficulties in electromagnetic delivery methods regarding the necessity of determining the field distribution in a complex tissue morphology to determine the intensity response characteristics (see page S95, left column, 2nd paragraph, for example). Otter et al disclose that their studies show that transmembrane signaling is part of the method by which the electromagnetic field interact with bone cells, but do not clarify how the fields alter the transmembrane flow of information (see page S98, right column, last paragraph). Otter teach that the

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possibility that pulsed electric fields affect receptors at the cell membrane surface is still under investigation (see page S100, left column, last paragraph, for example).

Further, Aaron et al (Clin. Orthop. Relat. Res. 2004, Vol. 419, pages 30-37) teach that electromagnetic fields enhance proliferation in preconfluent cell cultures, but that the interactions of physical forces, including electromagnetic fields, remain to be established (see page 30, right column, for example). Aaron et al teach that current therapeutic methods for delivering electric fields to cells would not depolarize cell membranes and would probably depend on a series of amplification mechanisms, such as acting through membrane receptors, or triggering calcium channels or enhancing interleukin receptors (see page 31, right column, 3rd paragraph, page 32, left column, and page 33, right column, 2nd paragraph for example). Aaron et al disclose recent observations from many laboratories indicate that electromagnetic fields can upregulate mRNA levels and protein synthesis or growth factors and that future studies will be needed to show changes in transcription, mRNA and protein synthesis. (see page 36, left column, last paragraph, in particular).

Simko and Mattsson (J. Cell Biochem. 2004, Vol. 3, pages 83-92) reviewed the state of the art regarding the effects of electromagnetic fields on cellular responses *in vitro*. Simko and Mattsson teach that a large number of cellular components, processes and systems are expected to be affected by electromagnetic field exposure and a large number of studies have been performed on processes such as cell cycle regulation. Simko and Mattsson disclose that electromagnetic field exposure also affects signal transduction processes such as Protein kinase C (PKC) signaling, which may regulate

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proliferation and differentiation. Simko and Mattsson disclose studies that suggest that electromagnetic field exposure can activate PKC together with TPA exposure, but alone does not cause PKC translocation (see page 85, left column, 1st paragraph).

Electromagnetic field exposure has been found to produce alterations in DNA and RNA synthesis along with effects on specific gene transcription; however, Simko and Mattsson teach that some of these results are not reproducible (see page 85, left column, 2nd paragraph). Simko and Mattsson teach that multiple *in vitro* studies have revealed that electromagnetic field delivery in frequency ranges of 50-100Hz has altered cell proliferation and affects the cell cycle specifically with regard to specific cell cycle parameters such as DNA synthesis and expression of cell cycle proteins such as cyclins and cdk. In contrast, Simko and Mattsson teach that other related studies demonstrated opposite effects of electromagnetic field delivery or no significant effect on DNA synthesis rates (see page 85, right column, 1st and 2nd paragraph). Simko and Mattsson propose that the wide variety of effects of electromagnetic field delivery to different cell types are dependent on cell age, differentiation status, activation state and metabolic state. Simko and Mattsson conclude that the evaluation of controversial electromagnetic field delivery results and verification of the studies to date are complicated by the fact that the effects of energy treatments are of small magnitude (see page 86, left column, 1st and 2nd paragraphs, in particular).

3) Unpredictability of the art. The unpredictability of a method for accelerating the cell cycle lies in the ability to deliver an effective amount of electromagnetic energy to accelerate the cell cycle or activate cell cycle regulators, transcription factors, signal

transduction proteins, DNA synthesis proteins or receptors, or inhibit an angiotensin receptor. The effective amount of any kind of electromagnetic energy for accelerating the cell cycle *in vivo* is not predictable in light of conflicting *in vitro* results as taught by Simko and Mattsson. In light of the teaching of Otter et al, one of skill in the art would recognize that there is additional complexity involved for a method comprising delivery of an effective amount of any type of electromagnetic energy to a cell *in vivo*, which is surrounded by other cells and tissues of varying properties such as density. Simko and Mattsson teach that some studies described effects of electromagnetic field exposure on cells but also that several observations have been difficult to replicate and in many studies no effect of electromagnetic field exposure is detected (see page 84, right column, 1st paragraph). Aaron et al teach that therapeutic use of biophysical techniques such as electromagnetic fields is largely empirical regarding dosing regimens because understanding of the interactions of such a technique with the cell membrane is limited (see page 36, left column, 2nd paragraph). Unpredictability of the claimed methods is also manifested in the ability to determine effective amounts of electromagnetic energy that would be able to activate a cell cycle regulator, or signal transduction protein or transcription factor or DNA synthesis protein, or receptor, or to inhibit an angiotensin receptor. A current method to determine changes in gene expression is microarray technology. However, Draghici et al (Trends Genet. 2006 Vol. 22, No. 2, Pages 101-9) teach that there are several limitations to microarray assays such as sensitivity, specificity and reproducibility, because all current technologies are based on a fundamental assumption that the microarray probes used produce specific signals

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under a single relatively permissive hybridization condition (see page 102, left column, 3rd paragraph). Draghici et al teach that accuracy and correctness of the identities of probe sequence in the arrays is a recognized problem (see page 101, right column, 2nd paragraph, for example). Draghici et al teach that the detection limit of current micro array technology is between one and ten copies of mRNA per cell, but may be insufficient to detect relevant changes in low abundance gene such as transcription factors (see page 103, left column, 3rd paragraph, in particular). Draghici et al further teach that while validation studies and control data sets allow for measurement of microarray accuracy, these measurements can only be applied to transcripts that are strongly expressed. Draghici et al teach the reproducibility of microarray data can be skewed by badly designed probes that can cross hybridize with multiple transcripts and give data that appears to be reproducible but is actually inaccurate (see page 105, right column, 1st paragraph). Draghici et al teach that experiment comparing three different microarray platforms revealed disappointing concordances in the ability to predict gene expression changes (see page 106, right column, 2nd paragraph). Draghici et al conclude that the reliable detection of low abundance genes are currently beyond the reach of microarray technology and the ability to detect changes in the expression of specific individual genes might be affected (see page 108, left column, 3rd paragraph). Therefore, the ability to deliver an effective amount of electromagnetic energy to a cell to activate or inhibit a receptor, or activate a signal transduction protein, or transcription factor or DNA synthesis protein is unpredictable in part, because state of the art methods to detect changes in expression, activation or inhibition of specific individual

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genes that might be in low abundance are not reliable so that the effective amount of electromagnetic energy required to activate or inhibit such proteins would be unpredictable.

4) Amount of guidance provided. The specification provides guidance regarding intensity and duration of energy for administration of radio frequency energy to an *in vitro* cell culture. The specification does not provide any guidance regarding the *in vivo* administration of radio frequency energy or any other type of electromagnetic energy. The specification does not provide any guidance regarding whether the cell cycle remains in an accelerated state or whether the cell cycle regulator, signal transduction protein, transcription protein, DNA synthesis protein, or receptor would remain in an activated state or whether the angiotensin receptor would remain inhibited after delivery of the energy. The specification does not address the possible ramifications related to sustained acceleration of the cell cycle or sustained activation or inhibition of cell cycle related proteins *in vivo*.

The specification discloses that parameters for delivering electromagnetic energy are adjustable with the stipulation that the cell being treated does not sustain substantial DNA damage. The specification discloses that useful power levels for the claimed method are in the range of about 1 to 300 mw/cm² (60 to 1,065 V/m). The specification discloses that the pulse rate can be in the range of about 100-3,600 ppm (pulses per minute), in the range of about 5-300 microseconds. The specification provides guidance on parameters for delivery of radio frequency energy that are effective for acceleration of the cell cycle for treatment of wounds including an average power level

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of about 15 mw/cm², 32 mw/cm², or 100 mw/cm² (about 240 V/m, 350 V/m or 600 V/m)

using pulse envelopes with a duration of about 32 msec at 1,000 pulses per second.

The disclosure states that radio frequency energy at about 30-40 mw/cm² (335-390

V/m) for a duration of about 16-20 msec at 1,200-1,500 pps is useful for treating

pressure ulcers, or at about 30-65 mw/cm² (335-500 V/m) for a duration of about 30-45

msec at 900-1,200 pps, or at about 30-100 mw/cm² (335-600 V/m) for a duration of

about 32-60 msec at 600-1,000 pps. The specification discloses that these parameters

with respect to wound healing can be used for stimulating cell proliferation, accelerating

the cell cycle, modulating the activity of a gene product. The disclosure states that an

effective treatment profile for wound healing includes delivery of electromagnetic energy

twice a day for thirty minutes per treatment with eight to twelve hours between

treatments. However, the specification does not provide guidance regarding

administration parameters for any other type of electromagnetic energy *in vivo* or *in vitro*

so that an effective amount would be delivered in order to accelerate the cell cycle or

activate a cell cycle regulator, a signal transduction protein, a transcription factor, a

DNA synthesis protein, a receptor or inhibit an angiotensin receptor. The specification

does not provide guidance regarding the administration of an effective amount of

electromagnetic energy to cells to accelerate the cell cycle *in vivo* when the cell cycle

has not been synchronized. The specification does not provide guidance regarding the

acceleration of the cell cycle for any other cell besides fibroblasts. The specification

does not provide guidance regarding how to determine an effective amount of any of the

claimed types of electromagnetic energy for specifically activating a cell cycle regulator.

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Applicants have not provided guidance on how to determine whether the electromagnetic energy has activated a specific cell cycle regulator such that it accelerates the cell cycle. The specification does not provide guidance regarding how to determine an effective amount of any of the claimed types of electromagnetic energy for specifically activating a signal transduction protein. The specification does not provide guidance regarding how to determine an effective amount of any of the claimed types of electromagnetic energy for specifically activating a transcription factor. The specification does not provide guidance regarding how to determine an effective amount of any of the claimed types of electromagnetic energy for specifically activating a DNA synthesis protein. The specification does not provide guidance regarding how to determine an effective amount of any of the claimed types of electromagnetic energy for specifically activating a receptor or inhibiting an angiotensin receptor.

5) Working examples. Applicants have provided an example of delivering radio frequency energy *in vitro* to primary human fibroblasts and epidermal keratinocytes. The cells had been chemically treated to synchronize the cell cycle and were released from synchronization before administration of the radio frequency energy. The radio frequency energy was administered at 32 mw/cm² in 42 msec pulses at a rate of 1 KHz for 30 minutes, which appeared to induce proliferation of the cells comparable to proliferation that occurs as a result of administration of platelet-derived growth factor. Applicants exemplify proliferation of untreated cells induced by administration of the media from the radio frequency energy treated cells. Applicants further exemplify increased expression levels of ERK-1 and ERK-2 compared to cells that had not been

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treated with radio frequency energy. Applicants exemplify that radio frequency energy treatment induced fibroblasts to enter the S phase of the mitotic cycle approximately eight hours before untreated control cells. Applicants suggest that these data indicate that radio frequency energy stimulates cell growth in a similar fashion as endogenous growth factors and that ERK activation after treatment indicates that the ERK kinase cascade is biologically relevant for affecting cell cycle progression and cell proliferation. The specification discloses microarray analysis of fibroblast and keratinocyte RNA expression levels following radio frequency energy treatment. Data exemplify that genes involved in regulation of the cell cycle and DNA synthesis were induced following radio frequency energy treatment including genes in delineated functional groups such as extracellular matrix receptors, transcription factors, signal transduction proteins, cell cycle regulators and DNA synthesis proteins.

6) Nature of the invention. The claimed methods are drawn to alteration of the cell cycle through alteration of cell signaling using electromagnetic energy, which are very complex and incompletely understood aspects of science and medicine.

7) Level of skill in the art. Given the scope of the claimed methods, the unpredictability of determining an effective amount of any kind of electromagnetic energy to be delivered to a cell *in vivo* or *in vitro* and the lack of guidance provided by the specification for the full scope of the claimed methods, one of a high level of skill in the art would have to practice undue trial and error experimentation to practice the claimed methods.

Given the above analysis of the factors which the Courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have practiced undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-9, 10-13, 15-18 and 20-24 are rejected under 35 U.S.C. 102(b) as being anticipated by George et al (U.S. Patent No. 6,334,069, 12/25/2001).

George et al teach a method of stimulating cellular growth and proliferation including reduction in cell doubling time in cells such as fibroblasts using an electromagnetic field of specified strength and duration. George et al teach that electromagnetic stimuli induces cell proliferation by reducing the G₀ and/or G₁ phases of the cell cycle by stimulating the genetic expression, release and functional

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enhancement of growth factors to increase the overall rate of proliferation in various cell types. George et al disclose that energy waves primarily defined as radio wave frequency are used *in vitro* and *in vivo* to induce cell proliferation in frequencies ranging from 1000Hz to 1000mHz to deliver an energy of 1 to 300 mW/cm² (see column 9, lines 12-65, in particular). The method taught by George et al reads on a method for accelerating the cell cycle comprising delivering an effective amount (e.g. 1 to 300 mW/cm²) for electromagnetic energy such as radio frequency to accelerate the cell cycle wherein the G1 phase of the cell cycle is shortened. George et al teach that the methods involve specific optimized dosages of pulsed electromagnetic energy (see column 10, lines 5-10, for example), which reads on a method for accelerating the cell cycle where the energy is pulsed. George et al teach that electromagnetic stimulation alters activity of cell cycle dependent proteins, inducing synthesis and activity of signal transduction molecules (see column 20, lines 1-7, for example), which reads on a method comprising delivering an effective amount of electromagnetic energy to activate a cell cycle regulator and a signal transduction protein. George et al teach that electromagnetic stimuli induces cell proliferation by stimulating the expression, release and functional enhancement of growth factors and inducing the flux of ions across cellular membranes and that a key component of the method is enhanced actions of fibroblast growth factors (see column 9, lines 20-30, for example). Absent evidence to the contrary, the electromagnetic stimuli used in this method would activate DNA synthesis proteins and a receptor. Given the reduction in cell doubling time the electromagnetic stimuli would increase the rate at which the cell replicates its DNA. The

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method taught by George et al also anticipates the claimed methods for activating a cell cycle regulator wherein the cell cycle regulator accelerates the cell cycle and for activating a signal transduction protein.

Claims 1-3, 5-9, 10-13, 15-18 and 20-24 are rejected under 35 U.S.C. 102(a) as being anticipated by George et al (U.S. Patent No. 6,353,763, 3/5/2002).

George et al teach a method of stimulating cellular growth and proliferation including reduction in cell doubling time in cells such as fibroblasts using an electromagnetic field of specified strength and duration. George et al teach that electromagnetic stimuli induces cell proliferation by reducing the G₀ and/or G₁ phases of the cell cycle by stimulating the genetic expression, release and functional enhancement of growth factors to increase the overall rate of proliferation in various cell types. George et al disclose that energy waves defined as radio wave frequency are used *in vitro* and *in vivo* to induce cell proliferation in frequencies ranging from 1000Hz to 1000mHz to deliver energy of 1 to 300 mW/cm² (see column 9, lines 14-65, in particular). The method taught by George et al reads on a method for accelerating the cell cycle comprising delivering an effective amount (e.g. 1 to 300 mW/cm²) for electromagnetic energy such as radio frequency to accelerate the cell cycle wherein the G₁ phase of the cell cycle is shortened. George et al teach that the methods involve specific optimized dosages of pulsed electromagnetic energy (see column 10, lines 6-15, for example), which reads on a method for accelerating the cell cycle where the energy is pulsed. George et al teach that electromagnetic stimulation alters activity of

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cell cycle dependent proteins, inducing synthesis and activity of signal transduction molecules (see column 20, lines 12-26, for example), which reads on a method comprising delivering an effective amount of electromagnetic energy to activate a cell cycle regulator and a signal transduction protein. George et al teach that electromagnetic stimuli induces cell proliferation by stimulating the expression, release and functional enhancement of growth factors and inducing the flux of ions across cellular membranes and that a key component of the method is enhanced actions of fibroblast growth factors (see column 9, lines 25-35, for example). Absent evidence to the contrary, the electromagnetic stimuli used in this method would activate DNA synthesis proteins and a receptor. The method taught by George et al also anticipates the claimed methods for activating a cell cycle regulator wherein the cell cycle regulator accelerates the cell cycle and for activating a signal transduction protein.

Claims 1-3, 5-9, 10-13, 15-18 and 20-24 are rejected under 35 U.S.C. 102(e) as being anticipated by George et al (U.S. Patent No. 6,353,763, filed 6/27/2000).

The applied reference has a common inventor (Frank R. George) with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

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The teachings of George et al (U.S. Patent No. 6,353,763) are described in the above rejection

Claims 1-3, 5-9, 10-13, 15-18 and 20-24 are rejected under 35 U.S.C. 102(e) as being anticipated by George et al (U.S. Patent No. 7,024,239, filed 11/20/2001).

The applied reference has a common inventor (Frank R. George) with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

George et al teach a method of stimulating cellular growth and proliferation including reduction in cell doubling time in cells such as fibroblasts using an electromagnetic field of specified strength and duration. George et al teach that electromagnetic stimuli induces cell proliferation by reducing the G₀ and/or G₁ phases of the cell cycle by stimulating the genetic expression, release and functional enhancement of growth factors to increase the overall rate of proliferation in various cell types. George et al disclose that radio wave frequencies are used *in vitro* and *in vivo* to induce cell proliferation in frequencies ranging from 1000Hz to 1000mHz to deliver energy of 1 to 300 mW/cm² (see column 9, lines 25-65 bridging to column 10, lines 1-15, in particular). The method taught by George et al reads on a method for accelerating

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the cell cycle comprising delivering an effective amount (e.g. 1 to 300 mW/cm²) for electromagnetic energy such as radio frequency to accelerate the cell cycle wherein the G1 phase of the cell cycle is shortened. George et al teach that the methods involve specific optimized dosages of pulsed electromagnetic energy (see column 10, lines 16-30, for example), which reads on a method for accelerating the cell cycle where the energy is pulsed. George et al teach that electromagnetic stimulation alters activity of cell cycle dependent proteins, inducing synthesis and activity of signal transduction molecules (see column 20, lines 19-32, for example), which reads on a method comprising delivering an effective amount of electromagnetic energy to activate a cell cycle regulator and a signal transduction protein. George et al teach that electromagnetic stimuli induces cell proliferation by stimulating the expression, release and functional enhancement of growth factors and inducing the flux of ions across cellular membranes and that a key component of the method is enhanced actions of fibroblast growth factors (see column 9, lines 35-45, for example). Absent evidence to the contrary, the electromagnetic stimuli used in this method would activate DNA synthesis proteins and a receptor. The method taught by George et al also anticipates the claimed methods for activating a cell cycle regulator wherein the cell cycle regulator accelerates the cell cycle and for activating a signal transduction protein.

Claim 27 is rejected under 35 U.S.C. 102(b) as being anticipated by Lenhardt and Ochs (U.S Patent No. 6,250,255, 6/26/2001).

Lenhardt and Ochs teach a method to activate a receptor comprising the step of producing pulsed microwave radiation to induce detectable changes in the inner ear, including thermoelastic expansion of fluids and structures in the inner ear, which activates receptors on hair cells (see column 2, lines 6-20, in particular). Lenhardt and Ochs teach that microwave pulses of a duration of 20 to 100 msec in an optimal frequency range of 0.9 to 4.0 Ghz is sufficient to generate a thermoelastic wave (see column 5, lines 60-67 bridging to column 6, lines 1-5, for example), which reads on a method for activating receptor comprising delivering to a cell an effective amount of electromagnetic energy to activate said receptor.

Claim 26 is rejected under 35 U.S.C. 102(b) as being anticipated by Yarosh (U.S. Patent No. 5,352,458).

Yarosh teaches a method of inducing melanogenesis in cells that have been contacted with a liposome containing a DNA repair enzyme and exposed to ultraviolet radiation. Yarosh teaches that DNA repair enzymes can include photolyases, DNA endonucleases, DNA helicases and base excision repair glycosylases (see column 3, lines 13-25, for example), which reads on a DNA synthesis protein. Yarosh teaches that UV exposure to cells can occur before, during or after the application of liposome comprising DNA repair enzymes (see column 4, lines 62-65, for example). Yarosh teaches that cells with liposomes containing a DNA repair enzyme were exposed to $\sim 100 \text{ J/m}^2$ of ultraviolet radiation and showed increased melanin production as a result of the radiation (see column 6, lines 25-67, for example). Yarosh teaches surprising

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results that DNA repair liposomes increase the amount of melanin produced by melanocytes (see column 4, lines 3-10, for example). The teaching of Yarosh reads on a method of activating a DNA synthesis protein by delivering an effective amount of electromagnetic energy (ultraviolet radiation) to the cell to activate said DNA synthesis protein.

Claims 15, 20 and 23-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Blumenberg (U.S. Patent Application Publication No. US2003/0073888, filed 09/06/2001).

Blumenberg teaches methods of detecting levels of RNA molecules in skin cells that have been exposed to ultraviolet radiation in which the total radiation energy exposure is 0.2 mJ/cm^2 to about 40 mJ/cm^2 (see paragraphs 0043-0045 and 0048, for example). Blumenberg teaches that cells to be used in the method are epidermal or dermal skin cells, keratinocytes, Langerhans cells, melanocytes or fibroblasts (see paragraph 085, for example). Blumenberg teaches that multiple DNA metabolism and repair enzymes including a novel growth factor receptor were upregulated by ultraviolet radiation exposure (see paragraph 0134 and Table 2 number 41, in particular).

Blumenberg teaches that multiple signal transduction proteins and transcription factors were upregulated several fold by ultraviolet radiation exposure (see paragraph 0136 and Table 3, in particular). Blumenberg teaches that ultraviolet radiation exposure induces expression of histones and DNA repair proteins and cyclins (see paragraphs 0257-0258, in particular). Blumenberg teaches that ultraviolet radiation exposure

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induces expression of multiple signal transduction proteins and transcription factors, including members of the Ras family and G protein subunits, phosphatases, immediate early genes such as c-fos, and also NF κ B transcription factor, for example (see paragraphs 0261-0265, in particular). Blumenberg teaches that ultraviolet radiation regulates the expression of DNA damage-inducible proteins such as cyclin G1 and these proteins play a role in cell cycle arrest (see paragraph 0258, which reads on a method for activating a cell cycle regulator by delivering an effective amount of electromagnetic energy to activate the regulator. The teaching of Blumenberg reads on methods of activating signal transduction proteins, transcription factors, DNA synthesis proteins and receptors by delivering to a cell an effective amount of electromagnetic energy in the form of ultraviolet radiation to activate said signal transduction proteins, transcription factors, DNA synthesis proteins and receptors.

Claim 24 is rejected under 35 U.S.C. 102(b) as being anticipated by Derijard et al (Cell, Vol. 76. pages 1025-1037).

Derijard et al teach that COS cells were transfected with an expression vector comprising a gene that encoded a novel protein kinase known as c-Jun NH₂ terminal kinase (JNK1). Derijard et al teach the cells were exposed to ultraviolet radiation and JNK1 was activated at 20 J/m² and maximally activated at 80 J/ m² (see page 1029, in particular), which reads on a method of activating a signal transduction protein.

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Claims 15 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al (Cancer Res., Vol. 56, pages 2510-2514).

Wang et al teach that cultured HeLa cells were irradiated with ultraviolet (UVC) energy with moderate dose of 10 and 30 J/m² and levels of a protein known as p16^{CDKN2A} (i.e. a cell cycle regulator) increased up to eight fold over control levels (see page 2510, right column, 1st, 2nd and 6th paragraph, for example), which reads on a method of activating a cell cycle regulator by delivering an effective amount of electromagnetic energy, in the form of ultraviolet radiation, to the cell.

Conclusion

No claims are allowed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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7/17/2006


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